CLAIMS

1. A fusion protein comprising a heat shock protein fused to a single epitope-containing segment, the epitope-containing segment comprising two or more identical self-epitopes.

2. The fusion protein of Claim 1 wherein the heat shock protein is ubiquitin and the fusion protein is a ubiquitin fusion protein.

3. The ubiquitin fusion protein of Claim 2 wherein the epitope-containing segment is fused to ubiquitin at a fusion site selected from the group consisting of the N-terminus, the C-terminus and an internal fusion site.

4. The ubiquitin fusion protein of Claim 2 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a second, unmodified ubiquitin protein.

5. The ubiquitin fusion protein of Claim 2 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a C-terminal ubiquitin subdomain competent to specify cleavage by a ubiquitin-specific protease between the C-terminal residue of the C-terminal ubiquitin subdomain and the N-terminal residue other than methionine.

6. The ubiquitin fusion protein of Claim 5 wherein at least one epitope-containing segment is positioned between the C-terminal residue of the C-terminal

ubiquitin subdomain and the N-terminal residue other than methionine, and the C-terminus of the C-terminal subdomain is modified to inhibit cleavage by a ubiquitin-specific protease.

7. The ubiquitin fusion protein of Claim 2 which is post-translationally modified by the addition of fatty acids to enhance immunogenicity.

8. The ubiquitin fusion protein of Claim 2 wherein the epitope-containing segment contains from about 2 to about 30 self-epitopes.

9. The ubiquitin fusion protein of Claim 2 wherein the identical self-epitopes are B-cell epitopes.

10. The ubiquitin fusion protein of Claim 2 wherein the identical self-epitopes are T-cell epitopes.

11. The ubiquitin fusion protein of Claim 2 wherein the identical self-epitopes are structural mimics of biomolecules.

12. The ubiquitin fusion protein of Claim 2 wherein the identical self-epitopes represent epitopes from the proteins selected from the group consisting of gonadotropin releasing hormone, tumor necrosis factor, immunoglobulins, chorionic gonadotrophin, inhibin, growth hormones and sperm proteins.

13. The ubiquitin fusion protein of Claim 2 wherein the identical self-epitopes are gonadotropin releasing hormone epitopes.

14. The ubiquitin fusion protein of Claim 13 wherein the epitope-containing segment is comprised of amino acids QHWSYGLRPGQHWSYGLRPG (SEQ ID NO: 26), and is inserted between position 35 and 36 of ubiquitin.

15. The ubiquitin fusion protein of Claim 13 wherein the epitope-containing segment is comprised of amino acids QHWSYGLRPGQHWSYGLRPGQHWSYGLRPGQHWSYGLRPGC (SEQ ID NO: 34) and is fused via its N-terminal amino acid to the C-terminal residue of ubiquitin, the ubiquitin fusion protein being cleavable by a ubiquitin specific protease.

16. The ubiquitin fusion protein of Claim 15 which is further conjugated to an immunogenic carrier protein.

17. The ubiquitin fusion protein of Claim 2 wherein the internal fusion sites comprises a region of ubiquitin linking two domains of secondary structure, the two domains of secondary structure being selected from the group consisting of β-strand and α-helix.

18. The ubiquitin fusion protein of Claim 2 wherein the epitope-containing segment is fused to the C-terminus of ubiquitin and the C-terminus of ubiquitin is modified to inhibit cleavage of the ubiquitin fusion protein by a ubiquitin-specific protease.

19. The ubiquitin fusion protein of Claim 18 wherein the C-terminus of ubiquitin is modified at amino acid 76.

20. The ubiquitin fusion protein of Claim 19 wherein the modification at amino acid 76 of ubiquitin is a substitution of an amino acid selected from the group

consisting of alanine, valine, and cysteine for the wild-type glycine amino acid residue.

21. The ubiquitin fusion protein of Claim 20 wherein the substituted amino acid is valine.

22. The ubiquitin fusion protein of Claim 21 wherein the epitope-containing segment comprises the amino acids sequence QHWSYGLRPGQHWSYGLRPGQHWSYGLRPGQHWSYGLRPG (SEQ ID NO: 35).

23. The ubiquitin fusion protein of Claim 22 which is further conjugated to an immunogenic carrier protein.

24. A fusion protein comprising a heat shock protein fused to two or more non-contiguous epitope-containing segments, each epitope-containing segment comprising one or more identical or non-identical self-epitopes.

25. The fusion protein of Claim 24 wherein the heat shock protein is ubiquitin and the fusion protein is a ubiquitin fusion protein.

26. The ubiquitin fusion protein of Claim 25 wherein the non-contiguous epitope-containing segments are fused to ubiquitin at fusion sites selected from the group consisting of the N-terminus, the C-terminus and internal fusion sites.

27. The ubiquitin fusion protein of Claim 25 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a second, unmodified ubiquitin protein.

28. The ubiquitin fusion protein of Claim 25 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a C-terminal ubiquitin subdomain competent to specify cleavage by a ubiquitin-specific protease between the C-terminal residue of the C-terminal ubiquitin subdomain and the N-terminal residue other than methionine.

29. The ubiquitin fusion protein of Claim 28 wherein at least one epitope-containing segment is positioned between the C-terminal residue of the C-terminal ubiquitin subdomain and the N-terminal residue other than methionine, and the C-terminus of the C-terminal subdomain is modified to inhibit cleavage by a ubiquitin-specific protease.

30. The ubiquitin fusion protein of Claim 25 which is post-translationally modified by the addition of fatty acids to enhance immunogenicity.

31. The ubiquitin fusion protein of Claim 25 wherein the epitope-containing segments contain from about 1 to about 30 self-epitopes.

32. The ubiquitin fusion protein of Claim 25 wherein one epitope-containing segment contains at least one epitope which is a B-cell epitope and one epitope which is a T-cell epitope.

33. The ubiquitin fusion protein of Claim 25 wherein one epitope-containing segment contains at least two epitopes which are B-cell epitopes.

34. The ubiquitin fusion protein of Claim 25 wherein one epitope-containing segment contains at least two epitopes which are T-cell epitopes.

35. The ubiquitin fusion protein of Claim 25 wherein one or more self-epitopes contained within the epitope-containing segments are structural mimics of biomolecules.

36. The ubiquitin fusion protein of Claim 26 wherein one or more self-epitopes contained within the epitope-containing segments represent self-epitopes from the group of proteins selected from the group consisting of gonadotropin releasing hormone, tumor necrosis factor, immunoglobulins, chorionic gonadotrophin, inhibin, growth hormones and sperm proteins.

37. The ubiquitin fusion protein of Claim 36 wherein one or more self-epitopes contained within the epitope-containing segments represent epitopes from gonadotropin releasing hormone.

38. The ubiquitin fusion protein of Claim 37 wherein there are two epitope-containing segments, each comprising two identical self-epitopes.

39. The ubiquitin fusion protein of Claim 38 wherein the first self-epitope-containing segment is fused to the C-terminal residue of ubiquitin via its N-terminal residue, and the second self-epitope-containing segment is fused at an internal fusion site which comprises regions of ubiquitin linking two domains of secondary structure selected from the group consisting of β-strand and α-helix.

40. The ubiquitin fusion protein of Claim 39 wherein the second epitope-containing segment is located between position 35 and 36 of ubiquitin.

41. The ubiquitin fusion protein of Claim 40 wherein the epitope-containing segments comprise the amino acid sequence QHWSYGLRPGQHWSYGLRPG (SEQ ID NO: 26).

42. The ubiquitin fusion protein of Claim 41 wherein the N-terminus of the N-terminal epitope-containing segment is further fused the C-terminal residue of a second ubiquitin protein, the ubiquitin fusion protein being cleavable from the first ubiquitin protein by a ubiquitin specific protease.

43. The ubiquitin fusion protein of Claim 26 wherein the internal fusion sites comprise regions of ubiquitin linking two domains of secondary structure, the two domains of secondary structure being selected from the group consisting of β-strand and α-helix.

44. The ubiquitin fusion protein of Claim 43 wherein the internal fusion site is between residue 35 and 36 of ubiquitin.

45. The ubiquitin fusion protein of Claim 46 wherein one epitope-containing segment comprises a single B-cell epitope or a plurality of identical or non-identical B-cell epitopes and a second epitope-containing segment comprises a single T-cell epitope or a plurality of identical or non-identical T-cell epitopes.

46. The ubiquitin fusion protein of Claim 26 wherein at least one epitope-containing segment is fused to the C-terminus of ubiquitin and the C-terminus of ubiquitin

is modified to inhibit cleavage of the ubiquitin fusion protein by a ubiquitin-specific protease.

47. The ubiquitin fusion protein of Claim 46 wherein the C-terminus of ubiquitin is modified at amino acid 76.

48. The ubiquitin fusion protein of Claim 47 wherein the modification at amino acid 76 of ubiquitin is a substitution of an amino acid selected from the group consisting of alanine, valine, and cysteine for the wild-type glycine amino acid residue.

49. A fusion protein comprising a heat shock protein fused to a single epitope-containing segment comprising two or more identical or non-identical self-epitopes, the epitope-containing segments being fused to the heat shock protein at fusion sites selected from the group consisting of the N-terminus and an internal fusion site.

50. The fusion protein of Claim 49 wherein the heat shock protein is ubiquitin and the fusion protein is a ubiquitin fusion protein.

51. The ubiquitin fusion protein of Claim 50 wherein the single epitope-containing segment contains from about 2 to about 30 identical or non-identical self-epitopes.

52. The ubiquitin fusion protein of Claim 50 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a second, unmodified ubiquitin protein.

53. The ubiquitin fusion protein of Claim 50 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a C-terminal ubiquitin subdomain competent to specify cleavage by a ubiquitin-specific protease between the C-terminal residue of the C-terminal ubiquitin subdomain and the N-terminal residue other than methionine.

54. The ubiquitin fusion protein of Claim 53 wherein at least one epitope-containing segment is positioned between the C-terminal residue of the C-terminal ubiquitin subdomain and the N-terminal residue other than methionine, and the C-terminus of the C-terminal subdomain is modified to inhibit cleavage by a ubiquitin-specific protease.

55. The ubiquitin fusion protein of Claim 50 which is post-translationally modified by the addition of fatty acids to enhance immunogenicity.

56. The ubiquitin fusion protein of Claim 50 wherein the epitope-containing segment contains at least one B-cell and one T-cell epitope.

57. The ubiquitin fusion protein of Claim 50 wherein the epitope-containing segment contains at least two B-cell epitopes.

58. The ubiquitin fusion protein of Claim 50 wherein the epitope-containing segment contains at least two T-cell epitopes.

59. The ubiquitin fusion protein of Claim 50 wherein the epitope-containing segment contains self-epitopes which are structural mimics of biomolecules.

60. The ubiquitin fusion protein of Claim 50 wherein the epitope-containing segment contains at least one self-epitope from proteins selected from the group consisting of gonadotrophin releasing hormone, tumor necrosis factor, immunoglobulins, proteins, chorionic gonadotrophin, inhibin, growth hormones and sperm proteins.

61. The ubiquitin fusion protein of Claim 50 wherein the epitope-containing segment contains self-epitopes from gonadotropin releasing hormone.

62. The ubiquitin fusion protein of Claim 50 wherein the internal fusion site comprises a region of ubiquitin linking two regions of secondary structure selected from the group consisting of β-strand and α-helix.

63. The ubiquitin fusion protein of Claim 50 wherein the epitope-containing segment contains a single B-cell epitope or a plurality of identical or non-identical B-cell epitopes and a second epitope-containing segment comprises a single T-cell epitope or a plurality of identical or non-identical T-cell epitopes.

64. A fusion protein comprising a heat shock protein fused to a single epitope-containing segment comprising one or more identical or non-identical self-epitopes, the epitope-containing segment being fused to the heat shock protein at the N-terminus of the heat shock protein.

65. The fusion protein of Claim 64 wherein the heat shock protein is ubiquitin and the fusion protein is a ubiquitin fusion protein.

66. The ubiquitin fusion protein of Claim 65 wherein the epitope-containing segment contains from about 1 to about 30 self-epitopes.

67. The ubiquitin fusion protein of Claim 65 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a second, unmodified ubiquitin protein.

68. The ubiquitin fusion protein of Claim 65 wherein the N-terminal residue of ubiquitin is a residue other than methionine, and the N-terminal residue other than methionine is fused to the C-terminal residue of a C-terminal ubiquitin subdomain competent to specify cleavage by a ubiquitin-specific protease between the C-terminal residue of the C-terminal ubiquitin subdomain and the N-terminal residue other than methionine.

69. The ubiquitin fusion protein of Claim 68 wherein at least one epitope-containing segment is positioned between the C-terminal residue of the C-terminal ubiquitin subdomain and the N-terminal residue other than methionine, and the C-terminus of the C-terminal subdomain is modified to inhibit cleavage by a ubiquitin-specific protease.

70. The ubiquitin fusion protein of Claim 65 which is post-translationally modified by the addition of fatty acids to enhance immunogenicity.

71. The ubiquitin fusion protein of Claim 65 wherein the epitope-containing segment contains at least one B-cell epitope and one T-cell epitope.

72. The ubiquitin fusion protein of Claim 65 wherein the epitope-containing segment contains at least two B-cell epitopes.

73. The ubiquitin fusion protein of Claim 65 wherein the epitope-containing segment contains at least two T-cell epitopes.

74. The ubiquitin fusion protein of Claim 65 wherein one or more self-epitopes contained within the epitope-containing segment is a structural mimic of a biomolecule.

75. The ubiquitin fusion protein of Claim 65 wherein one or more self-epitopes contained within the epitope-containing segment represent a self-epitope from the group of proteins selected from the group consisting of gonadotropin releasing hormone, tumor necrosis factor, immunoglobulins, chorionic gonadotrophin, inhibin, growth hormones and sperm proteins.

76. The ubiquitin fusion protein of Claim 75 wherein one or more self-epitopes contained within the epitope-containing segment represent a self-epitope from gonadotropin releasing hormone.

77. The ubiquitin fusion protein of Claim 65 wherein the epitope-containing segment contains a single B-cell epitope or a plurality of identical or non-identical B-cell epitopes and a second epitope-containing segment

comprises a single T-cell epitope or a plurality of identical or non-identical T-cell epitopes.

78. A DNA construct encoding the fusion protein of Claim 1, 24, 49, or 64.

79. A DNA construct encoding the fusion protein of Claim 14, 15, 22, 41, or 42.

80. A cell containing a DNA construct encoding the fusion protein of Claim 1, 24, 49, or 64.

81. A cell containing a DNA construct encoding the fusion protein of Claim 14, 15, 22, 41, or 42.

82. A method for stimulating an immune response in an animal, the immune response being directed toward a self-antigen, the method comprising:

a) providing a ubiquitin fusion protein comprising ubiquitin fused to one or more contiguous or non-contiguous epitope-containing segments, the epitope-containing segments comprising two or more identical or non-identical self-epitopes; and

b) administering the fusion protein of step a) to an animal under conditions appropriate for the stimulation of an immune response.

83. The method of Claim 82 wherein the ubiquitin fusion protein of step a) is conjugated to an immunogenic carrier protein prior to administration.

84. The method of Claim 82 wherein fusion of the epitope-containing segments to ubiquitin occurs at site(s) selected from the group consisting of the C-terminus, the N-terminus, and an internal site of ubiquitin.

85. The method of Claim 84 wherein one epitope-containing segment is fused to ubiquitin and the fusion site is the C-terminus of ubiquitin.

86. The method of Claim 85 wherein the epitope-containing segment fused to the C-terminus of ubiquitin is cleavable by a ubiquitin-specific protease.

87. The method of Claim 85 wherein the ubiquitin moiety is modified such that the epitope-containing segment fused to the C-terminus of ubiquitin is non-cleavable by a ubiquitin-specific protease.

88. The method of Claim 84 wherein the self-antigen is a peptide hormone.

89. The method of Claim 88 wherein the peptide hormone is a male-specific or female-specific peptide hormone.

90. The method of Claim 89 wherein the peptide hormone is gonadotropin releasing hormone.

91. The method of Claim 90 wherein the physiological consequences of administration to the animal are substantially similar to the consequences of surgical castration.

92. The method of Claim 91 wherein the animal is a pig.

93. The method of Claim 90 wherein one epitope-containing segment which comprises the amino acid sequence QHWSYGLRPGQHWSYGLRPG (SEQ ID NO: 26) is fused to ubiquitin between positions 35 and 36 of the ubiquitin amino acid sequence.

94. The method of Claim 90 wherein two non-contiguous epitope-containing segments, each comprising the amino acid sequence QHWSYGLRPGQHWSYGLRPG (SEQ ID NO: 26) are fused to a single ubiquitin molecule, one being fused to the N-terminal amino acid of ubiquitin, the other being fused at an internal site of ubiquitin, the internal site being between residue 35 and 36 of ubiquitin.

95. The method of Claim 87 wherein one epitope-containing segment which comprises the amino acid sequence QHWSYGLRPGQHWSYGLRPGQHWSYGLRPGQHWSYGLRPG (SEQ ID NO: 35) is fused via its N-terminus to the C-terminal residue of ubiquitin.

96. The method of Claim 86 wherein one epitope-containing segment which comprises QHWSYGLRPGQHWSYGLRPGQHWSYGLRPGQHWSYGLRPGC (SEQ ID NO: 34) is fused via its N-terminus to the C-terminal residue of ubiquitin.

97. A method for stimulating an immune response in an animal, the immune response being directed toward a ubiquitin fusion protein, the method comprising:

a) providing a ubiquitin fusion protein comprising ubiquitin fused to a single epitope-containing segment, the epitope-containing segment comprising two or more identical epitopes;

b) administering the fusion protein of step a) to an animal under conditions appropriate for the stimulation of an immune response.

98. A method for stimulating an immune response in an animal, the immune response being directed toward a ubiquitin fusion protein, the method comprising:

a) providing a ubiquitin fusion protein comprising ubiquitin fused to two or more non-contiguous epitope-containing segments, each epitope-containing segment comprising one or more identical or non-identical epitopes;

b) administering the fusion protein of step a) to an animal under conditions appropriate for the stimulation of an immune response.

99. A method for stimulating an immune response in an animal, the immune response being directed toward a ubiquitin fusion protein, the method comprising:

a) providing a ubiquitin fusion protein comprising ubiquitin fused to a single epitope-containing segment comprising two or more identical or non-identical epitopes, the epitope-containing segments being fused to ubiquitin at fusion sites selected from the group consisting of the N-terminus and an internal fusion site;

b) administering the fusion protein of step a) to an animal under conditions appropriate for the stimulation of an immune response.

100. A method for stimulating an immune response in an animal, the immune response being directed toward a ubiquitin fusion protein, the method comprising:

a) providing a ubiquitin fusion protein comprising ubiquitin fused to a single epitope-containing segment comprising one or more identical or non-identical epitopes, the epitope-containing segment being fused to ubiquitin at N-terminus of ubiquitin;

b) administering the fusion protein of step a) to an animal under conditions appropriate for the stimulation of an immune response.

101. A method for stimulating an immune response in an animal, the immune response being directed toward a self-antigen, the method comprising:
   a) providing a DNA construct encoding the fusion protein of Claim 1, 24, 49 or 64;
   b) introducing the DNA construct of step a) into the cells of the animal under conditions appropriate for expression.

102. A method for the identification of antibodies in experimental or diagnostic samples, comprising:
   a) providing a ubiquitin fusion protein selected from the group consisting of ubiquitin fusion proteins described in Claims 1, 24, 49 and 64;
   b) providing antibodies from an experimental or clinical source;
   c) forming an incubation mixture comprising the ubiquitin fusion protein of step a) and the antibodies of step b); and
   d) detecting binding of the antibodies of step b) to the ubiquitin fusion protein of step a).

103. A method for reducing levels of a predetermined endogenous protein in an animal relative to base-line levels, comprising:
   a) providing a ubiquitin fusion protein selected from the group consisting of ubiquitin fusion proteins described in Claim 1, 24, 49 and 64, the ubiquitin fusion protein containing at least one self-epitope representing an epitope from the predetermined endogenous protein; and
   b) administering the fusion protein of step a) to the animal under conditions appropriate for the stimulation of an immune response.

104. The method of Claim 103 wherein the predetermined endogenous protein is a peptide hormone.

105. The method of Claim 104 wherein the predetermined endogenous peptide hormone is a male-specific or female-specific peptide hormone.

106. The method of Claim 105 wherein the predetermined endogenous peptide hormone is gonadotropin releasing hormone.

107. The method of Claim 103 wherein the predetermined endogenous protein is tumor necrosis factor.

108. The method of Claim 103 wherein the predetermined endogenous protein is a growth hormone protein.

109. The method of Claim 103 wherein the fusion protein is conjugated to a non-ubiquitin carrier protein.

110. A method for reducing levels of a predetermined endogenous protein in an animal relative to base-line levels, comprising:

a) providing a DNA construct encoding a ubiquitin fusion protein selected from the group consisting of ubiquitin fusion proteins described in Claim 1, 24, 49 and 64, the ubiquitin fusion protein containing at least one self-epitope representing an epitope from the predetermined endogenous protein; and

b) introducing the DNA construct of step a) into the cells of an animal under conditions appropriate for expression and stimulation of an immune response.

111. The method of Claim 110 wherein the predetermined endogenous protein is a peptide hormone.

112. The method of Claim 111 wherein the predetermined endogenous peptide hormone is a male-specific or female-specific peptide hormone.

113. The method of Claim 112 wherein the predetermined endogenous peptide hormone is gonadotropin releasing hormone.

114. The method of Claim 110 wherein the predetermined endogenous protein is tumor necrosis factor.

115. The method of Claim 110 wherein the predetermined endogenous protein is a growth hormone protein.

116. The method of Claim 110 wherein the fusion protein is conjugated to a non-ubiquitin carrier protein.